REMARKS

Claims 1-21 are canceled. Claim 22 is amended. Claims 22-50 remain active and under consideration.

Independent claim 22 has been amended to recite a method which is used to quantify the BER and NER activities of a biological medium. This amendment is provided to merely clarify the claimed invention and is not intended as a narrowing amendment.

In addition this claim has been further modified so as to specify the nature of the biological medium which is being tested, specifically this biological medium is a purified or unpurified biological preparation from a subject. This is a also a clarifying amendment.

The various components of the repair solution have also been amended so as to more clearly specify the essential components namely at least one biological medium and labelled nucleotide triphosphates; and also to specify other optional components, namely one or more enzymes involved in DNA repair, ATP an ATP-regenerating system. These are also clarifying amendments.

Support for all of these amendments can be found in the specification as filed and therefore no new matter has been added by way of these amendments.

Scope of amended claim 22

The scope of claim 22 has been further defined and the components and steps of the claimed method/assay have been further defined as well.

In particular the claimed method has been restricted to one which assays BER and NER activities simultaneously, rather than to an assay of the more general DNA repair properties of a biological medium.

As pointed out above the nature of the biological medium which is the subject of this assay has also been unambiguously defined as being a purified or unpurified cellular extract preparation from the subject of the assay.

Further, as pointed out in the previous response this biological medium may be prepared in accordance with paragraph 100 of the present specification, that is according to the method set out in Manley et al., 1983, Methods Enzylmol. 101, 568-582 or according to Biade et al., 1998, J. Biol. Chem., 273, 898-902 or according to any other method. In particular the biological medium is prepared from a sample containing cells from an individual; the biological medium contains DNA repair proteins from a subject in an active form (if these are present in an active form in the sample).

The effects of these active proteins are then tested by incubating them in combination with the repair solution upon a functionalised support onto which have been disposed a series of lesion containing supercoiled DNA plasmids.

The essential components of the repair solution have also been unambiguously listed in amended claim 22, as have the optional components of the repair solution.

The ability of the subject to repair DNA damage via the NER and BER mechanisms are therefore assessed by the method according to claim 22.

Amended claim 22 therefore provides a specific assay for the assessment of the NER and BER DNA repair properties of a biological medium, which is combined with a repair solution and incubated with one or a series of pretreated supercoiled DNA plasmids which comprise a number of lesions and which are attached to a

functionalised support in a number of discrete zones. By the action of the biological medium the repair of these lesions is quantitatively assessed by monitoring the amount of labelled nucleotides which are incorporated into the 'repaired' DNA plasmids.

As well as allowing a quantitative assessment of the NER and BER DNA repair capacity of a sample, because a number of important human diseases are associated with an individual having faulty DNA repair systems such as xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy, this assay allows therefore can be used to diagnose the basis of a pathology presented by a patient.

Claim Rejections – 35 USC § 112

Claims 22-50 stand rejected under 35 USC 112, second paragraph.

Given the amendments to claim 22, it is submitted that this claim and each of claims 23 to 50 as dependent thereon meet the requirements of § 112, particularly as to definiteness.

With specific reference to the examiners comments and summation in the middle paragraphs of page 3, the following additional comments are provided.

Claim 22 is amended so as to explicitly recite the essential components of the repair solution, namely the labelled nucleotide triphosphates and the biological medium. The repair of the target lesion containing-supercoiled-plasmid DNA targets by the incorporation of the labelled nucleotides occurs via the action of the active components present in the biological medium. As pointed out in the previous response, it also possible that the biological medium will have no (or very little) NER/BER activity and so no repair of the target DNA molecules may occur, leading to no measurable incorporation of the labelled nucleotides.

Also as pointed out above, the biological medium is now specified in claim 22 as being obtained from an individual and therefore the examiner's concerns that the results of the assay would not provide information concerning the DNA repair capacity of an individual is incorrect. It is also point out that the claimed method does not study the individual's DNA but the DNA repair properties of an individual's active proteins.

Hence, this ground of rejection is deemed moot.

Claim Rejections – 35 USC § 103

Claims 22-25, 29, 31, 33, 33, 38, 41-44, 47 and 50 stand rejected under 35 USC 103(a) as being unpatentable over **US 2002/0022228** in view of **Calsou et al**.

Claims 26-28 stand rejected under 35 USC 103(a) as being unpatentable over **US 2002/0022228** and **Calsou et al** in further view of **Douki et al**.

Claim 30 stands rejected under 35 USC 103(a) as being unpatentable over **US 2002/0022228** and **Calsou et al** and further in view of **MPEP 2144.05**.

Claims 34-36 stand rejected under 35 USC 103(a) as being unpatentable over **US 2002/0022228** and **Calsou et al** in further view of **Chu et al**.

Claims 32 and 37 stand rejected under 35 USC 103(a) as being unpatentable over **US 2002/002228** and **Calsou et al** in view of **Zierdt et al**.

Claims 39 and 40 stand rejected under 35 USC 103(a) as being unpatentable over **US 2002/0022228** and **Calsou et al** in further view of **Gelfand et al**.

Claims 45 and 46 stand rejected under 35 USC 103(a) as being unpatentable over **US 2002/0022228** and **Calsou et al** in further view of **MPEP 2144.05**.

Claim 48 stands rejected under 35 USC 103(a) as being unpatentable over **US 2002/0022228** and **Calsou et al** in further view of **Yershov et al**.

Claim 49 stands rejected under 35 USC 103(a) as being unpatentable over **US 2002/0022228** and **Calsou et al** in further view of **Randerath et al**.

However, none of the cited references, either alone or in combination, describes or suggests the claimed invention.

Applicant notes that the examiner has reiterated the previous obviousness rejection that claim 22 would have been obvious to one skilled in the art based upon a combination of the previously cited **US 2002/0022228 ('228)** and **Calsou et al.**, JBC, 1996 (Calsou).

In the present and previous Official Action the examiner appears to have accepted Applicant's arguments that '**228** does not deny novelty or obviousness to the claimed invention in combination with any of the previously cited prior art documents, because none of '228 or any of these other documents even suggest the use of a lesion containing DNA target molecule which is supercoiled.

The examiner has alleged that this feature of a supercoiled DNA target is known from **Calsou** and so the skilled man would have arrived at the method according to claim 22 by combining the teaching of '**228** and **Calsou**.

In the previous response we urged that the examiner reconsider the reasoning behind the combination of these prior art documents as it appeared that the examiner was performing an *ex post facto* (or hindsight reasoning) analysis in phrasing the question/problem solved by the invention, in particular including the feature that the target DNA was supercoiled. Yet, clearly, this could only have come from a knowledge of the claimed invention that the skilled man on December 20, 2002, when this Patent Application was filed simply did not have.

In response to our arguments on page 6 the examiner stated that "any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning."

But the approach suggested by the examiner is contrary to that that proposed in § 706.02 (j) to 706.02 (n), 2106 to 2107, 2141 to 2146 and 2163 of the MPEP.

Herein the question of nonobviousness must be determined as of the "time the invention was made." And the use of hindsight or evaluation in the context of skills developed by the evaluator or skilled artisan after the date of the invention have no place and must be ignored in the determination of nonobviousness.

Importantly, the U.S. Supreme Court in *KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. 398 (2007) reaffirmed the framework for determining obviousness as set forth in *Graham v. John Deere*. The basic factual inquiries of *Graham v. John Deere* are: (1) determining the scope and contents of the prior art; (2) ascertaining the differences between the prior art and the claims in issue; and (3) resolving the level of ordinary skill in the art while taking into account secondary considerations.

The Supreme Court in *KSR* noted that the key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. This may be either due to an explicit teaching in the prior art or

based on the common sense of the artisan as supported by the prior art. Thus, there still must be support in the prior art under either theory of obviousness.

By formulating the question addressed by the present invention so as to include features which the inventors have proven to be essential to the present invention, but which were not known or thought to be so at the time this invention was made, the examiner has contaminated the obviousness analysis by essentially providing the answer to the question in the question and so rendering its solution therefore obvious. This is the very definition of impermissible hindsight reconstruction.

The unbviousness of amended claim 22

As noted above however claim 22 has been further modified and these further modifications to the claimed method clearly make this subject matter unobvious with respect to the prior art. Claim 22 has in particular been modified so as to explicitly specify that the claimed method assesses both NER and BER activities in a single assay.

With reference to the plurality of prior art references cited by the examiner during the prosecution of this Patent Application, it is pointed out that none of the prior art documents teach the use of supercoiled DNA for assays of NER activity and that none of the prior art documents teach that it is possible to test both NER and BER activity in a single assay.

Use of Supercoiled DNA for NER assays

As argued at length in the record, and apparently accepted by the examiner, on the whole the prior art describes methods to ascertain DNA repair using non-supercoiled DNA. Based upon the prior art document **Calsou**, this evaluation of the teaching of the

prior art is no longer valid for assays of DNA repair *per se*, but is still valid for assays of the NER component of DNA repair and reference is made to our previous argumentation upon this point.

Combined NER/BER assays

As explained in our previous response, on page 1 paragraphs [0012] to [0020] of the present specification, the DNA excision and resynthesis repair systems of an organism comprise two main pathways Base Excision Repair (BER) and Nucleotide Excision Repair (NER). BER and NER act through different enzymes upon different types of lesions/mutations, with BER acting to repair damage to a single base such as when the base becomes oxidised, alkylated or deaminated and NER acting to repair larger damage such as base pair dimer formation and 6-4 photoproducts. The main enzymes involved in BER are DNA glycosylases and AP endonucleases; the main enzymes involved in NER are XPA, XPB, XPC, XPD, XPE, XPF, XPG, ERCC1, RPA, Rad23, CSA and CSB.

Of the various prior art documents cited by the examiner, the majority such as '**228** deal with NER whilst **Calsou** deals with BER.

All of the cited prior art references therefore relate to methods to assay different types of lesion repair mechanisms related to either NER or BER. Given the differences in lesion specificity shown by the NER and BER mechanisms and the molecular mechanisms underlying the repair of these disparate lesion types teaching relating to NER or BER cannot be combined as evidenced by the lack of cross teaching in the cited prior art.

In accordance with the teaching of the present specification and to show that this specification provides all the teaching necessary to put a combined NER/BER assay into practice, the present specification describes an example of such an assay in which; upon the same functionalised support a supercoiled DNA target treated with UV-C and

a supercoiled DNA target treated with endoperoxide $DHPNO_2$, can be positioned within one or more of the zones (A_1 to A_x). These different supercoiled DNA targets will comprise different lesions (amongst others, nucleotide base dimers in the case of the UV-C treated DNA target and oxidised bases in the case of the endoperoxide $DHPNO_2$ treated DNA target). Therefore by monitoring the incorporation of label into these different targets, the NER and BER activities of the biological sample can be determined simultaneously.

No prior art document or documents, therefore teach the simultaneous global (NER and BER) quantitative assessment of excision and resynthesis repair or suggest that this is possible.

Amended Claim 22 involves an unobvious step

As indicated above the different BER and NER mechanisms of DNA repair occur via different enzymatic pathways and act upon different types of lesions. NER and BER therefore represent distinct mechanisms of DNA repair and the combination of teaching relating to these different mechanisms is not an obvious undertaking.

In a review of the cited prior art, we find no teaching or suggestion that a NER assay using supercoiled DNA was possible or desirable and therefore the method according to amended claim 22 is inventive at least in respect of this aspect of its scope.

Further the present inventors have shown for the first time that a single reaction upon assorted DNA targets can be used to assay NER and BER activity simultaneously.

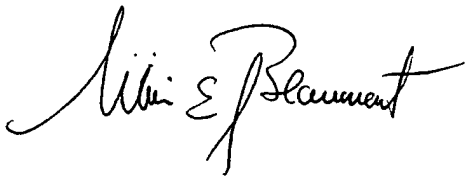
Clearly, no prior art document or documents of record discloses or suggests that this simultaneous quantitative global (NER and BER) assessment detection of excision and resynthesis repair is possible.

That differently treated supercoiled DNA targets can be combined in this way, so as to assess both the NER (for which the use of supercoiled DNA targets is unknown) and the BER capacity of a biological sample is therefore not obvious with respect to the cited prior art.

Thus, all of the above prior art grounds of rejections are believed to be unsustainable and should be withdrawn.

Accordingly, in view of all of the above, it is believed this application is now in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,



William E. Beaumont
Reg. No. 30,996
Juneau Partners